REMARKS

The Office Action

Claims 1-18 are pending. Claims 1, 2, 12, 15, and 17 stand rejected for indefiniteness. Claims 1-18 stand rejected for obviousness over Greenwell (LE Magazine, May 2000) in view of Weiss (Life Sciences 1995, 56: 637-660), Renshaw et al. (U.S. Patent No. 5,958,896; hereafter "Renshaw") and Katzung (*Basic & Clinical Pharmacology*, Appleton, 1998).

Support for the Amendments

Claim 8 has been reworded at the request of the Office. Support for new claim 19 is found in claim 13 (M.P.E.P. § 2173.05(i)). Support for new claim 20 is found in claim 15.

Claim Objections

Claim 8 is objected to for reciting "administering" rather than "administration." Although the metes and bounds of the original claim are apparent, claim 8 has been amended as requested by the Office.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 2, 12, 15, and 17 stand rejected for indefiniteness. Applicants traverse this rejection.

The purpose of the definiteness requirement is to ensure that "the scope of the claim is clear to a hypothetical person possessing the ordinary skill in the pertinent art" (M.P.E.P. § 2171). Furthermore, M.P.E.P. § 2173.02 states:

> Definiteness of claim language must be analyzed, not in a vacuum, but in light of:
> (A) The content of the particular application disclosure;
> (B) The teachings of the prior art; and
> (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

In addition, "[b]readth of a claim is not to be equated with indefiniteness" (M.P.E.P. § 2173.04). Each of the terms rejected in the instant claims is definite under this standard, and Applicants emphasize that the specification is not required to recite a definition for a term that is used in a manner consistent with its art-known meaning.

Regarding claim 1, the Office states that "the meaning of the term 'normalizing' [the sleep/wake cycle of a mammal] is unclear in light of the specification." The basis for this rejection is the Office's assertion that one may be asleep while working, the relevance of which to the term "normalizing" is unclear to Applicants.[1] The term "normalize" means "to make conform to or reduce to a norm or standard" (Merriam-Webster Online Dictionary). In addition, the term "sleep/wake cycle" is an art-known term denoting a mammal's pattern of being awake and being asleep. Thus, "normalizing the sleep/wake cycle of a mammal" simply means making the sleep/wake pattern of a

1 For the record, Applicants do not agree that napping while physically at work constitutes proof that one may be asleep while working. Furthermore, Applicants' reference to "sleeping during the day and working at night" is one *example* of a sleep/wake cycle where the individual involved works the night shift and therefore sleeps during the day; this *example* does not imply that "working" and "awake" are synonymous.

mammal conform to its norm or standard, the parameters of which are well known to practitioners in this field. Furthermore, some mammals are diurnal (i.e., active during the day), some are nocturnal (i.e., active during the night), and others are some combination of the two; thus, the norm or standard will depend on the individual mammal. All of these things would be readily understood by one of skill in the art, and the rejection of the claims based on the term "normalizing the sleep/wake cycle" may be withdrawn.

Claim 2 stands rejected for reciting the terms "fatigue," "tiredness," and "sleep quality." It is unclear on what basis the Office has rejected these terms, as each is used in the instant claims consistently with its ordinary meaning. "Fatigue" and "tiredness" are well-known terms, common in everyday usage and in the medical field. For example, Greenberg, "Clinical Dimensions of Fatigue" *Primary Care Companion J Clin Psychiatry* 2002 4:90-93, a copy of which is enclosed, discusses various medical aspects of fatigue and illustrates the term's art-known meaning. Tiredness is also a commonly used term whose meaning is well known to the skilled artisan and the common man. The Office's reliance on the possibility of someone to "contrive" a new meaning for fatigue or tiredness is misplaced. Claim terms are interpreted in light of their meaning to one of ordinary skill in the art, and not on the ability to fabricate a new definition. Furthermore, the fact that fatigue and tiredness are generic for physical and mental states does not render the terms indefinite: "[b]readth is not to be equated with indefiniteness" (M.P.E.P. § 2173.04).

"Sleep quality" is also an art recognized term. For example, Shargel et al., provided by the Office, recites, "Sleep time and quality of sleep vary widely among individuals" (pg. 547). Like Shargel et al., the specification draws a distinction between the quantity of sleep and the quality of sleep in the recited definition of "sleep quality," and reference to "actual rest" in this definition is merely to highlight the difference between quantity and quality of sleep, no matter the underlying physiological mechanism. Thus, the definition of "sleep quality" recited in the specification is consistent with the art-known meaning of the term, and the rejection may be withdrawn.

Claims 1 and 12 stand rejected for reciting a "therapeutically-effective amount." The basis for this rejection is that "[t]he specification provides no reference points from which to measure a therapeutically effective amount." Applicants disagree. The instant specification defines "therapeutically-effective amount" on page 4 as "an amount ... sufficient to produce a healing, curative, prophylactic, stabilizing, or ameliorative effect in a mammal suffering from a sleep disorder, an abnormal sleep/wake cycle, or sleep deprivation." The specification further illustrates two methods for determining the effectiveness of administering a compound: (1) measurement of levels of activity (see Figure 1) and (2) visual analog scores provided by the patient (see Figure 2). Furthermore, the specification on page 11 provides general guidelines for preferred amounts of compounds, e.g., "50 mg per day to 2000 mg per day." Based on the specification, one skilled in the art could readily determine a therapeutically effective amount. This rejection may also be withdrawn.

Regarding the recitation of "problem sleepiness" in claim 15, Applicants enclose a copy of "Facts about Problem Sleepiness," published in September 1997 by the National Institutes of Health. This reference shows that "problem sleepiness" is an art-used term, and no further definition is required. The ability of the Office to "construe" additional meanings is unavailing. This basis for the § 112 rejection may also be withdrawn.

Finally, the Office has rejected claim 17 for reciting "cognitive function," again because there is no definition in the specification, and the Office has construed multiple meanings for the term. "Cognitive function" is an art-used term whose metes and bounds are apparent to one skilled in the art. As evidence of the art usage, Applicants note that the phrase "cognitive function" was found in 4563 references on PubMed prior to the December 20, 2002 priority date for the instant application (a copy of the search is enclosed). As the term is routinely used in the art, this rejection may also be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-18 stand further rejected for obviousness over Greenwell in view of Weiss, Renshaw, and Katzung. Applicants traverse this rejection.

Each of independent claims 1, 12, and 17, from which the remaining claims depend, requires the administration of a cytidine-containing compound, a cytosine-containing compound, a uridine-containing compound, a creatine-containing compound, an adenosine-containing compound, or an adenosine-elevating compound to a mammal either to (1) normalize the mammal's sleep/wake cycle (claim 1), (2) treat the mammal's

sleep disorder (claim 12), or (3) increase cognitive function in a sleep-deprived mammal (claim 17).

In rejecting the instant claims, it appears that the Office has assigned meanings to the claim terms, with which Applicants disagree. In claim 1, the term "normalizing" means making the sleep/wake cycle of a mammal conform to a norm or standard. This term is not equivalent with "maintaining sleep" by decreasing sensory input as disclosed in Greenwell. The term "therapeutically effective amount" is defined in the specification as "an amount ... sufficient to produce a healing, curative, prophylactic, stabilizing, or ameliorative effect in a mammal suffering from a sleep disorder, an abnormal sleep/wake cycle, or sleep deprivation" and not as "any amount that maintains sleep." The terms "fatigue" and "tiredness" have their art accepted meaning, which is not "the state of falling asleep." One may be fatigued or tired and not falling asleep. As discussed above, "sleep quality" is an art known term that refers to the amount of rest achieved from sleeping, as opposed to the amount of time spent asleep, and the term is not equivalent to "sleep that is not light sleep." "Problem sleepiness" is a condition that should be interpreted in accordance with the guidelines promulgated by the NIH. Finally, "cognitive functioning" means brain function associated with cognition, and not brain function in general.

To support an obviousness rejection, the Office must put forth a *prima facie* case that meets the legal standard for obviousness found in M.P.E.P. § 2142. This section states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

This standard has not been met in the present case. The combined references fail to teach or suggest the invention, and there is no motivation to combine the cited references.

As stated above, the three independent claims require the administration of one of several classes of compounds, a cytidine-containing compound, a cytosine-containing compound, a uridine-containing compound, a creatine-containing compound, an adenosine-containing compound, or an adenosine-elevating compound, for one of three uses:

(1) Claim 1 and its dependent claims require that the administration result in the *normalization of the sleep/wake cycle* of a mammal;

(2) Claim 12 and its dependent claims require that the administration *treat a sleep disorder* in a mammal; and

(3) Claim 17 and its dependent claim require that the administration *increase cognitive function in a sleep-deprived mammal.*

Each of these uses has a connection to lack of proper sleep, but Applicants emphasize that, in order to support a *prima facie* case of obviousness, the prior art *must*

teach or suggest the administration of one of the *recited compounds* for the *specific use* recited in the claims. The combined references do not.

The Office primarily relies on Greenwell to teach or suggest the limitations of the instant claims. Greenwell, however, relates to the use of choline or choline-containing compounds for enhancing cognitive function. As noted by the Office, Greenwell states that choline is required for the synthesis of acetylcholine, which is "vital for thought, memory, and sleep." Greenwell further teaches that acetylcholine helps "maintain" sleep, but only in the context of "making it possible to sleep through minor noises and other distractions." None of these teachings suggest the limitations of any of the instant claims because they relate to the use of choline, and *not* a cytidine-containing compound, a cytosine-containing compound, a uridine-containing compound, a creatine-containing compound, an adenosine-containing compound, or an adenosine-elevating compound, as recited by the instant claims. Indeed, the only mention in Greenwell of a cytidine-containing compound is found at page 3, where the reference states: "Glyceryl-phosphorylcholine has also been compared with CDP-choline (cytidine diphosphocholine), and has been found to produce superior results in patients with vascular dementia. Another study found much higher plasma choline levels after injections of glyceryl-phosphorylcholine than CDP-choline." Thus, this passage mentions only CDP-choline and only in the context of vascular dementia. Greenwell does not teach or suggest the use of CDP-choline, or any other compound recited in the instant claims, in the context of normalizing the sleep/wake cycle, treating a sleep disorder, or increasing

the cognitive function of a sleep-deprived mammal. Applicants further emphasize that "maintaining sleep" and "decreasing the chance of becoming a light sleeper" are not equivalent to either normalizing the sleep/wake cycle, as recited in claim 1, or increasing cognitive function in a sleep deprived mammal, as recited in claim 17.

Nothing in Weiss remedies the deficiencies of Greenwell. The Office relies on Weiss for the teaching that CDP-choline contains cytidine (which Applicants readily concede) and that the metabolism of CDP-choline results in formation of acetylcholine. Weiss is silent with respect to any use of CDP-choline for any sleep related use and therefore does not teach or suggest that CDP-choline is useful for normalizing the sleep/wake cycle, treating a sleep disorder, or increasing the cognitive function of a sleep-deprived mammal, as recited by the instant claims.

The Office has cited Renshaw in further support of the rejection of claims 12-14, but this reference also fails to remedy the deficiencies of Greenwell. Renshaw teaches the use of CDP-choline and other compounds for treating a mammal exposed to a stimulant. Nowhere, however, does Renshaw suggest that such a treatment would be effective for treating a *sleep disorder* associated with substance abuse. Indeed, the term "sleep" does not appear in Renshaw.

In rejecting the instant claims, the Office has combined three references to teach or suggest the limitations. Each of the instant claims recites a limitation relating to sleep – normalizing the sleep/wake cycle; treating a sleep disorder; and increasing cognitive function in a sleep-deprived mammal. The instant claims also require the administration

of one of several classes of compounds. In contrast, two of the references relied on by the Office do not mention sleep, and the third, while discussing sleep, suggests the administration of compounds not recited in the instant claims. These references when combined simply do not suggest all of the limitations of the instant claims.

In addition to the failure of the combined references to teach or suggest the claims, there is also no motivation to combine or modify the references cited. As stated in M.P.E.P. § 2142, the Office has the burden "to provide some suggestion of the desirability of doing what the inventor has done." In this case, the Office only purports to provide motivation to combine references for the normalization of the sleep/wake cycle, as recited in claim 1. Since claims 12 and 17 are not directed to the normalization of the sleep/wake cycle, the Office has failed to meet its burden to establish a *prima case* of obviousness for those claims.

Regarding claim 1, the sole basis for motivation provided by the Office is that Greenwell teaches that choline functions to "maintain sleep," and Katzung teaches that users undergoing withdrawal from stimulants become sleepy. With regards to maintaining sleep, Greenwell only teaches that choline reduces sensory input, "making it possible to sleep through minor noises and other disturbances." Since Katzung teaches that stimulant withdrawal leads to sleepiness, as opposed to the inability to sleep discussed in Greenwell, one would not be motivated to administer choline to anyone suffering from stimulant withdrawal. In fact, one would be motivated to avoid administration of choline to subjects suffering from stimulant withdrawal, since

"maintaining sleep" would lead to the subjects falling asleep instead of making the subjects more awake.

Greenwell also discusses the use of choline, not a cytidine-containing compound, a cytosine-containing compound, a uridine-containing compound, a creatine-containing compound, an adenosine-containing compound, or an adenosine-elevating compound, as required in the instant claims. Furthermore, Greenwell clearly teaches that CDP-choline is not a preferred compound, thereby failing to provide motivation to employ CDP-choline for any use. Thus, even if there was motivation to combine Greenwell and Katzung (which there is not), such a combination would not lead one skilled in the art to administer any of the compounds required in the instant claims.

In sum, the Office does not attempt to provide motivation for two of the independent claims. For claim 1, the motivation provided is to administer a compound to increase sleep in a population that is already prone to sleep. Such motivation is not based on sound scientific reasoning or logic, as required by law, and the rejection may be withdrawn.

CONCLUSION

Applicants submit that claims are in condition for allowance, and such action is respectfully requested. Enclosed is a Petition to extend the period for replying for three months, to and including June 16, 2005, and a check in payment of the required extension

fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Karen L. Elbing, Ph.D.
Reg. No. 35,238

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045